The epidemiology of aplastic anemia in Thailand

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Aplastic anemia has been linked to environmental exposures, from chemicals and medical drugs to infectious agents. The disease occurs more frequently in Asia than in the West, with incidence rates 2- to 3-fold higher. We report updated results of an epidemiologic study conducted in Thailand from 1989 to 2002, in which 541 patients and 2261 controls were enrolled. Exposures were determined by in-person interview. We observed significantly elevated relative risk estimates for benzene (3.5) and other solvents (2.0) and for sulfonamides (5.6), thiazides (3.8), and mebendazole (3.0). Chloramphenicol use was infrequent, and no significant association was observed. Agricultural pesticides were implicated in Khonkaen (northeastern Thailand). There were significant associations with organophosphates (2.1), DDT (6.7), and carbamates (7.4). We found significant risks for farmers exposed to ducks and geese (3.7) and a borderline association with animal fertilizer (2.1). There was a significant association in Khonkaen with drinking other than bottled or distilled water (2.8). Nonmedical needle exposure was associated in Bangkok and Khonkaen combined (3.8). Most striking was the large etiologic fraction in a rural region accounted for by animal exposures and drinking of water from sources such as wells, rural taps, and rainwater, consistent with an infectious etiology for many cases of aplastic anemia in Thailand. (Blood. 2006;107: 1299-1307)

Introduction

Aplastic anemia (AA) is defined as pancytopenia accompanied by a hypocellular bone marrow.[1] Laboratory and clinical observations have implicated an immunologic pathophysiology. As with other autoimmune diseases, both environmental triggers and individual host factors are hypothesized to determine risk. AA has long been linked to exposure to benzene, pesticides, and other chemicals.[2] Marrow failure is a severe idiosyncratic complication of the use of certain medical drugs, most infamously chloramphenicol.[2] It can follow specific viral infections, as in postseronegative hepatitis,[3] and it is a rare complication of pregnancy.[4] Clusters of AA have been reported.[5-8] Nevertheless, mechanisms linking environmental triggers to bone marrow failure are poorly defined, and most cases are labeled idiopathic.

While rare in the United States and Europe, AA occurs more frequently elsewhere. Early Western observers were struck by the large numbers of cases they observed in Asian clinics.[9,10] Japanese hematologists have commented on AA as an unusual diagnosis in Europe and the United States.[11] Large numbers of AA cases have been reported from single hospitals in China,[12] Korea,[13] Thailand,[14] and elsewhere in Asia.[15-19] Early estimates suggest that AA was at least 4- to 5-fold more common in the East[20,21]; autopsy diagnoses were 3-fold higher in Japan compared to Europe and the United States.[22] An extraordinarily high prevalence was reported for specific locations (the Mudanjiang region of China[23]) and in certain populations (industrial workers in Japan[24]). Exposure to toxic chemicals was implicated; other potential culprits were hepatitis and common, casual administration of the antibiotic chloramphenicol.[25]

Starting in the late 1980s, we undertook a systematic epidemiologic study of AA in Thailand to determine a precise incidence rate and risk factors, reasoning that etiologic environmental exposures could be more easily identified where the disease was prevalent. Using an active case-ascertainment strategy based on previous experience conducting the International Agranulocytosis and Aplastic Anemia Study (IAAAS) in Europe and Israel[26] and concentrating on metropolitan Bangkok and the 2 rural regions of Songkla and Khonkaen, we found that AA was 2- to 3-fold more frequent in these areas of Thailand than in the West.[27,28] A questionnaire was employed to identify differences in recent environmental histories between aplastic anemia patients and a comparative series of other hospital patients selected to be representative of the entire population. Prominent reported findings from the early phase of the study included surprising associations of AA with poverty[29] and rice farming[30] and with agricultural[30] but not household[31] pesticide use. There was also a low proportion of cases in which medical drug use could be implicated.[32] As risk factors were identified or discarded based on these results, the geographic compass of the study and the focus of the questionnaire were refined. We here report final results obtained from the Thai study—the largest collection of AA cases ever subjected to systematic analysis—with particular emphasis on more recently collected information.

Patients, materials, and methods

A case-control study was carried out in 2 phases: from February 1989 to December 1994 (phase 1), and from January 1995 to March 2002 (phase 2).

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Protocols were approved by institutional review boards of Mahidol University, Khonkaen University, Prince of Songkla University, the National Heart, Lung, and Blood Institute, and Boston University. All patients and controls provided informed consent according to the Declaration of Helsinki.

Phase 1

The study commenced in Bangkok (including the city and the suburbs of Nonthaburi, Nakornpathom, Patumthani, Samutprakarn, and Samutsakorn: total population approximately 8.75 million) in February 1989. In November 1991, it was expanded to the Khonkaen region in northeastern Thailand (Khonkaen, Kalasin, Mahasarakam, Loei, Nongkai, Udonthani, and Royed: 7.64 million) and to the Songkla region in the south (Songkla, Yala, Pattani, Satoon, Nakornsrithammarat, and Trang: 4.99 million). The study was population based in all participating centers.[27]

In each region, potential cases were identified by regular contact with hematologists or other physicians either by telephone or visit at least every other week. Eligible subjects were required to meet at least 2 of the following criteria: white blood cell count 3.5×10^9/L, platelet count equal to or less than 50×10^9/L, and either hemoglobin concentration equal to or less than 100 g/L or hematocrit equal to or less than .30 (30%). If the latter criterion was 1 of 2 fulfilled, a reticulocyte count equal to or less than 30×10^9/L also was required. Patients who received chemotherapy, immunotherapy, or radiotherapy were excluded. Fanconi anemia also was excluded, based on family history and the presence of typical physical characteristics. The definitive diagnosis and final acceptance of cases also required a characteristic bone marrow biopsy showing hypocellularity without fibrosis or infiltration by leukemic, lymphomatous, or carcinoma cells. The biopsies were reviewed by study hematologists without knowledge of exposures to determine final eligibility.

Controls were selected from among other hospital patients and matched to potential cases for age (younger than 2, 2-5, 6-14, 15-24, 25-44, 45-64, and at least 65 years) and sex in an approximate ratio of 4:1. To maximize the number of controls, those matched to excluded potential cases were retained in the analysis. To be eligible, controls had to have admission diagnoses judged to be independent of drug use or occupational exposure. Acceptable diagnoses included trauma, acute infections (eg, pneumonia), acute abdominal emergencies (such as appendicitis), and other selected conditions (eg, cataract surgery). As with cases, patients who had received chemotherapy, immunotherapy, or radiotherapy were excluded.

All subjects were interviewed by trained study personnel who were physicians or nurses, and all interviewers enrolled both cases and controls. The information included demographic data; relevant medical history; detailed history of drug use (including herbal preparations), focusing especially on the 6 months before admission; history of pesticide use, again with emphasis on the 6 months before admission; and history of exposure to chemicals or radiation. There were no refusals to participate among the potential cases and controls. All cases were included in the estimation of incidence rates, but some were too ill to be interviewed. A total of 374 cases were identified, of which 284 were interviewed, including 160 in Bangkok, 81 in Khonkaen, and 43 in Songkla. Interviewed cases were somewhat younger (37% under the age of 25) and more likely to be male (53%) than those who were not interviewed (29% and 48%, respectively). There were 1174 controls (Bangkok, 698; Khonkaen, 295; Songkla, 181). The diagnostic distribution of the controls included 310 (26%) with trauma, 232 (20%) with acute infections, 257 (22%) with abdominal emergencies, and 375 (32%) with other diagnoses.

Phase 2

In phase 2, data collection was expanded or modified to pursue in greater detail potential leads identified in phase 1. However, care was taken to ensure that the data from the 2 phases could, when appropriate, be combined. For practical reasons Songkla was no longer included as a study center, and in Bangkok data collection was restricted to one hospital (Siriraj). In Khonkaen the hospital network remained unchanged; thus, the study encompassed the full population of that region during phase 2.

During phase 2, greater detail on occupational and household exposure to solvents and other chemicals and on recent job history was recorded. Data collection also was expanded to obtain information relevant to a possible infectious etiology, as suggested by results of phase 1, including the nonmedical use of needles, sanitary facilities, source of drinking water, and farming practices; the latter included the crops farmed and farming methods. In 1998 further questions were added to obtain information on exposure to farm animals and fertilizers.

A total of 257 cases was enrolled, 77 in Bangkok and 180 in Khonkaen. There were 1087 controls (317 and 770, respectively), with a diagnostic distribution of 505 (46%) with trauma, 218 (20%) with acute infections, 190 (18%) with abdominal emergencies, and 174 (16%) with other diagnoses.

Data analysis

Relative risks (odds ratios) were estimated by unconditional logistic regression[33] to control confounding. Crude relative risk estimates also are provided for all comparisons, but unless otherwise specified the multivariate estimates are referred to in describing results. Different models were used in various subanalyses, as described later in this section. As a check on the homogeneity of the controls, sensitivity analyses also were conducted, in which major categories of controls were excluded in turn from the multivariate models evaluating the main risk factors. The results generally were consistent with those based on all the controls, and only the latter are reported.

Results concerning drug use have been reported previously, based on phase 1 data.[32] To update those findings, the combined data from the entire study were used, including 541 cases and 2261 controls. For the analysis of solvent exposures the data also were combined. Factors included in the models for these analyses were the matching variables (age, sex, and region), year of interview (as a continuous variable), and the use of drugs, solvents, and occupational and household pesticides (the latter for control of confounding only).

For all other factors, data analysis was confined to phase 2. This included factors previously reported and now evaluated further (income[29] and pesticides[31]) and newly explored potential risk factors (farming, exposure to farm animals, fertilizer use, consumption of raw fish and crabs, nonmedical needle exposures, sanitation, and drinking water). Risks for needle exposures were estimated based on the total phase 2 dataset of 257 cases and 1087 controls, with the following additional factors in the model: age, sex, region, year of interview (as a continuous variable), and occupational and household pesticide use. Risks according to income and source of drinking water in Bangkok were estimated based on 77 phase 2 cases and 317 controls, from models which included age, sex, and year of interview in addition to the specific factors under consideration.

There were more factors under consideration in the Khonkaen phase 2 analyses of 180 cases and 770 controls (pesticides, other farming variables, sources of drinking water, and income), and the models were correspondingly more complex. In addition to the specific factor(s) under consideration, the models included age, sex, year of interview (as a continuous variable), residential location within the Khonkaen region (4 categories of urban and rural areas), occupational and household pesticide use, exposure to ducks or geese, use of animal fertilizers, and consumption of nonbottled water.

Etiologic fractions representing the proportion of the disease attributable to exposure were calculated for significantly associated factors.[34]

Results

Demographic characteristics (total study data)

Age and sex distributions of cases and controls were similar in each of the 3 regions due to matching (Table 1). There were slightly more males than females among the cases in Bangkok, an even split in Khonkaen, and a preponderance of females in Songkla (with a much smaller total number). The cases from Bangkok were

Table 1. Distribution of 541 cases of aplastic anemia and 2261 controls by region according to age and sex

	Cases		Controls	
	No.	%	No.	%
Bangkok (237 cases, 1015 controls)				
Age younger than 25 years	103	43	418	41
Age 25 to 39 years	64	27	258	25
Age 40 to 59 years	42	18	179	18
Age at least 60 years	28	12	160	16
Male	126	53	527	52
Female	111	47	488	48
Khonkaen (261 cases, 1065 controls)				
Age younger than 25 years	41	16	173	16
Age 25 to 39 years	73	28	322	30
Age 40 to 59 years	99	38	402	38
Age at least 60 years	48	18	168	16
Male	129	49	544	51
Female	132	51	521	49
Songkla (43 cases, 181 controls)				
Age younger than 25 years	9	21	33	18
Age 25 to 39 years	4	9	27	15
Age 40 to 59 years	10	23	41	23
Age at least 60 years	20	47	80	44
Male	17	40	90	50
Female	26	60	91	50

younger: median age was 26 years, compared with 43 years in Khonkaen and 57 years in Songkla.

Socioeconomic status (phase 2)

Self-reported per capita household income was used as an index of socioeconomic status. In an earlier finding from phase 1 of the study, we reported an inverse association of income with increasing relative risk of AA.[29] In the more recent sample from phase 2, this association was no longer observed either in Bangkok or in Khonkaen (Table 2). For the lowest income group (< 1000 baht/mo, adjusted for inflation to 1989 baht to be comparable with the phase 1 results) in Khonkaen, a crude relative risk estimate of 2.1 was reduced by multivariate adjustment to 1.1; the main factors accounting for the reduction were residential location and consumption of nonbottled water.

Benzene and other solvents (total study data)

For benzene the overall relative risk estimate was 3.5 (95% CI, 1.2-10), and for cumulative exposure of at least 4 days, it was 3.2 (1.0-11) (Table 3). For fuels (kerosene, gasoline, fuel oil, and diesel fuel) and glues, there were no associations. For other solvents, mostly unspecified thinners, the overall estimate of 2.0 was significantly elevated, and for at least 4 days of total exposure the estimate was 1.9 (1.2-2.8). Turpentine was the specific chemical most often identified (phase 2 only): while the overall prevalence was higher among cases (5% vs 2%), the prevalence of at least 4 days' exposure was similar (1% vs 1%).

Medical drugs (total study data)

We previously reported that the proportion of AA that could be attributed to drug use in Thailand was low.[32] In the full study data, there were few exposures to chloramphenicol; the relative risk estimate of 1.8 was not statistically significant (Table 4), although the upper confidence limit was 6.5. For sulfonamides (all taken as anti-infectives), the estimate was 5.6 (1.4-22). For mebendazole and thiazides, the estimates were 3.0 (1.2-7.8) and 3.8 (1.6-9.4), respectively. For nonsteroidal anti-inflammatory drugs (NSAIDs), the relative risk estimate was 1.6 and nonsignificant. No other associations were uncovered in the combined data (results not shown). There were no reported exposures to gold or penicillamine.

Pesticides (phase 2, Khonkaen)

An emphasis in phase 2 was agricultural exposures. For their evaluation, the analysis was confined to Khonkaen, a predominantly rural area. We previously reported that, with the possible exception of insecticides in the carbamate class, household pesticide use does not increase the risk of AA,[31] and the phase 2 data from Khonkaen confirmed this lack of association (Table 5). Specifically for household carbamates, there were 27 exposed cases (15%) and 115 exposed controls (15%). Risks were elevated for several different classes of agricultural pesticides. Overall, for organophosphates, the relative risk estimate was 2.1 (1.1-4.2), comparable to the results from phase 1.[30] For DDT, based on small numbers, the estimate was 6.7 (1.5-30). For carbamates, the estimate was 7.4 (1.7-31), but there were only 3 exposed controls. For paraquat, an herbicide, the relative risk estimate was 2.3

Table 2. Per capita household income among 257 cases of aplastic anemia and 1087 controls according to region (phase 2 data only)

	Cases		Controls		Relative risk estimate	
Per capita income, baht/mo*	No.	%	No.	%	Crude	Multivariate (95% CI)†
Bangkok; 77 cases, 317 controls						
At least 5000	40	52	131	41	1.0‡	1.0‡
2500 to 4999	19	25	110	35	0.6	0.6 (0.3-1.0)
1000 to 2499	15	19	52	16	0.9	1.0 (0.5-1.9)
Less than 1000	2	3	15	5	0.5	0.5 (0.1-2.2)
Unknown	1	1	9	3	—	—
Khonkaen; 180 cases, 770 controls						
At least 5000	19	11	93	12	1.0‡	1.0‡
2500 to 4999	30	17	137	18	1.1	0.8 (0.4-1.5)
1000 to 2499	68	38	394	51	0.8	0.4 (0.2-0.7)
Less than 1000	62	34	146	19	2.1	1.1 (0.6-2.1)
Unknown	1	0.6	0	0	—	—

— indicates not calculated.

*Adjusted for inflation to 1989 baht.

†The following factors were included in the models: Bangkok: age, sex, year of interview (continuous term), consumption of nonbottled water, income; Khonkaen: age, sex, residential location, year of interview (continuous term), pesticide use, exposure to ducks, animal fertilizer use, consumption of nonbottled water, income.

‡Reference category.

Table 3. Solvent exposure among 541 cases of aplastic anemia and 2261 controls

	Cases		Controls		Relative risk estimate†	
Solvent*	No.	%	No.	%	Crude	Multivariate‡ (95% CI)
Benzene	7	1	8	0.3	3.7	*3.5* (1.2-10)
At least 4 days' total exposure	5	1	7	0.3	3.0	3.2 (1.0-11)
Fuels§	11	2	49	2	0.9	1.0 (0.5-2.0)
At least 4 days' total exposure	9	2	47	2	0.8	0.8 (0.4-1.8)
Glues‖	39	7	128	6	1.3	1.2 (0.7-1.8)
At least 4 days' total exposure	23	4	83	4	1.2	1.0 (0.6-1.7)
Other solvents¶	58	11	140	6	1.8	*2.0* (1.4-2.8)
At least 4 days' total exposure	40	7	106	5	1.7	*1.9* (1.2-2.8)

*Use in the year before admission. Categories not mutually exclusive.

†Relative to nonexposure to the solvent under consideration.

‡The following factors were included in the model: age, sex, region, year of interview, solvent exposure, pesticide use, drug use. Statistically significant estimates are italicized.

§Kerosene (7 cases, 23 controls), gasoline (5 cases, 24 controls), fuel oil (1, 2), diesel fuel (0, 4).

‖Tra chang glue (22 cases, 75 controls), rubber glue (3, 15), leather shoe glue (1, 6), PVC blue (0, 7), polyvinyl acetate (0, 2), epoxy (0, 2), unspecified glue (13, 26). Type of glue was not recorded in phase 1; identified nonsolvent-based glues were not included in the phase 2 portion of the data. A total of 33 cases and 123 controls were exposed to solvent-based glues in phase 2 (crude relative risk estimate, 1.2).

¶Turpentine (12 cases, 24 controls: reported in phase 2 only), naphtha (2, 0), paint remover (1, 0), 3A thinner (0, 6), alcohol (1, 7), toluene (1, 1), methylethylketone (1, 0), dry-cleaning solvent (0, 2), unspecified thinner (43, 111), unspecified solvent (5, 12).

(1.0-5.1). For the combined category of other occupational pesticides, there was no association. Subanalyses for each group of agricultural pesticides were conducted according to cumulative exposure and whether the pesticide was applied by the subject. The relative risk estimate for organophosphates was somewhat higher than the overall estimate when the compounds were applied by the subject (2.9). For cumulative exposure of at least 4 days, the estimate was similar to the overall (2.1). For DDT and carbamates, most exposures were in the "heavier" categories.

Farm animals, fertilizers, and other farming practices (phase 2, Khonkaen)

Farming practices were examined in phase 2 because the incidence of AA previously had been found to be higher in Khonkaen than in Bangkok and because we observed an association with rice farming. Here the analysis was confined to Khonkaen farmers and their families. There was no evidence of association for exposure to cattle, water buffalo, or chickens (Table 6). For exposure to ducks or geese, the relative risk estimate was 3.7 (1.6-8.1). For exposure to pigs, the point estimate was 2.5 but nonsignificant. More detailed information concerning the amount of care and number of animals maintained was unrevealing, as no material relationships were observed across categories of these factors (data not shown); in particular, the estimate for keeping at least 10 ducks was 3.9. For the use of animal fertilizers, the relative risk estimate was 2.1 (1.0-4.4), while for chemical fertilizers the prevalence of exposure was similar in cases and controls. Although there was not a clear relationship with type of animal fertilizer, more cases than controls used duck or pig waste.

Other farming practices and dietary habits among farmers also were examined. There were no statistically significant elevations in risk for eating raw (point estimate 2.0, 95% CI, 0.7-5.9; 7 cases, 10 controls), cooked, fermented, or salted crabs and fish obtained from the fields (data not shown). Other practices evaluated and also not found to be associated included eating rats from the field and type of footwear used (almost entirely barefoot or sandals) (data not shown). We also evaluated specific types of farming based on crop, and there was considerable overlap. There were adequate data for risk estimates for rice, cassava, and sugarcane only. Rice was predominant, and the overall relative risk estimate was 0.6 (0.4-1.0; 77 exposed cases, 300 exposed controls), in contrast to the positive association that we observed in phase 1, based on less-detailed information.[35] For cassava, the relative risk was 4.5 (1.8-11; 13 cases, 13 controls). For sugarcane (8 exposed cases, 29 exposed controls; crude relative risk estimate, 1.2), there was no association. For other individual crops the data were scanty, with no more than 4 cases in each group.

Water and sanitary facilities (phase 2)

Sources of drinking water were identified in phase 2. Findings differed for Bangkok and Khonkaen and are presented separately (Table 7). In Bangkok, relative to the use of bottled or distilled water only, drinking water from other sources carried a relative risk of 1.0 (0.6-1.8), and there

Table 4. Drug exposure in days 29 to 180 among 541 cases of aplastic anemia and 2261 controls

	Cases		Controls		Relative risk estimate*		
Drug	No.	%	No.	%	Crude	Multivariate† (95% CI)	Original relative risk estimate‡
Chloramphenicol	4	0.7	8	0.4	2.1	1.8 (0.5-6.5)	2.7 (0.7-10)
Sulfonamides	5	1	4	0.2	5.3	*5.6* (1.4-22)	*7.9*¶
Tetracyclines	10	2	23	1	1.8	1.6 (0.7-3.4)	1.8 (0.6-5.6)
Mebendazole	8	1	10	0.4	3.4	*3.0* (1.2-7.8)	*6.3*¶
Thiazide diuretics	10	2	11	0.5	3.9	*3.8* (1.6-9.4)	*7.7* (1.5-40)
NSAIDs	9	2	20	1	1.9	1.6 (0.7-3.8)	Not reported

*Relative to nonexposure to the drug under consideration.

†The following factors were included in the model: age, sex, region, year of interview, solvent exposure, pesticide use, drug use. Statistically significant estimates are italicized.

‡"Original relative risk estimates" are taken from the previously published findings of phase 1.[42]

¶Crude estimate with $P < .05$; the confidence interval was not provided.

Table 5. Pesticide use among 180 cases of aplastic anemia and 770 controls in Khonkaen (phase 2 data only)

	Cases		Controls		Relative risk estimate*	
Pesticide	No.	%	No.	%	Crude	Multivariate† (95% CI)
Organophosphates‡	21	12	32	4	3.0	*2.1* (1.1-4.2)
Applied by subject	15	8	16	2	4.4	*2.9* (1.3-6.9)
At least 4 days' total exposure	17	9	26	3	3.0	2.1 (1.0-4.4)
DDT	5	3	4	0.5	5.5	*6.7* (1.5-30)
Applied by subject	5	3	4	0.5	5.5	—
At least 4 days' total exposure	5	3	4	0.5	5.5	—
Carbamates§	8	4	3	0.4	12	*7.4* (1.7-31)
Applied by subject	7	4	2	0.3	—	—
At least 4 days' total exposure	6	3	1	0.1	—	—
Paraquat	12	7	24	3	2.2	2.3 (1.0-5.1)
Applied by subject	7	4	17	2	1.8	1.7 (0.6-4.7)
At least 4 days' total exposure	7	4	20	3	1.6	1.9 (0.7-4.9)
Other occupational pesticides‖	11	6	32	4	1.5	1.0 (0.4-2.2)
Applied by subject	6	3	18	2	1.5	0.7 (0.2-2.2)
At least 4 days' total exposure	9	5	24	3	1.6	1.1 (0.4-2.7)
Any household pesticides	64	36	238	31	1.2	1.3 (0.9-1.9)

— indicates not calculated.

*Relative to nonexposure to the pesticide under consideration.

†The following factors were included in the model: age, sex, residential location, year of interview (continuous term), pesticide use, exposure to ducks, animal fertilizer use, consumption of nonbottled water. Statistically significant estimates are italicized.

‡Methyl parathion (19 cases, 32 controls), omethoate (1 case), methalamidophos (1 case).

§Methomyl (6 cases, 1 control), carbofuran (2, 2), carbaryl (1, 0).

‖Glyphosate (3 cases, 23 controls), karate (3, 0), spark (1, 1), 2,4-D (1, 1), spato (1, 0), filatan (1, 0), supercorn (1, 0), endrin (0, 1), unspecified insecticide (2, 9), unspecified rodenticide (2, 1), unspecified fungicide (0, 1), unspecified herbicide (0, 1).

were no significant associations with specific sources. In Khonkaen, most cases and controls obtained drinking water from nonbottled sources; compared with those who drank bottled or distilled water only, the relative risk estimate was 2.8 (1.3-5.9), and it was even higher when income also was included in the model (3.3). The point estimates for specific sources of nonbottled water ranged from 2.6 to 3.8, all statistically significant. In both Bangkok and Khonkaen, more than 90% of cases and controls reported use of flush toilets with septic tanks, and there were no significant associations with AA (data not shown).

Needles (phase 2)

Nonmedical needle exposures (tattoos, body piercing, and acupuncture) were examined in phase 2. Only 8 cases and 10 controls reported exposure, but the overall relative risk estimate was 3.8 (1.5-10). No information was requested on intravenous drug use or HIV infection.

Hepatitis and other diseases (total study data)

Medical history of hepatitis and jaundice, tuberculosis, rheumatoid arthritis, malaria, and worms in the stool was obtained throughout the course of the study. There were no significant associations (data not shown). In the combined data from phases 1 and 2, there were only 2 cases ($< 1\%$) of apparent posthepatitis AA.

Discussion

Evidence for a higher rate of AA in Asian countries than in the West has come from diverse sources, not all of equal reliability, and

Table 6. Exposure to animals and fertilizers among farmers in Khonkaen (phase 2 data only)

	Cases		Controls		Relative risk estimate*	
Exposure	No.	%	No.	%	Crude	Multivariate† (95% CI)
Farm animals						
Cattle or water buffalo	30	45	79	33	1.7	1.2 (0.6-2.4)
Chickens	29	44	68	29	2.0	1.0 (0.5-2.0)
Ducks or geese‡	17	26	18	8	4.2	*3.7* (1.6-8.1)
Pigs	5	8	5	2	3.8	2.5 (0.6-10)
Fertilizer§						
Chemical	46	70	161	68	1.1	—
Animal‖	18	27	30	13	2.6	2.1 (1.0-4.4)
Compost	0	0	1	0.4	—	—

Questions added in March, 1998; information available for 66 cases and 238 controls.

— indicates not calculated.

*Relative to nonexposure to the factor under consideration.

†The following factors were included in the model: age, sex, residential location, year of interview (continuous term), pesticide use, exposure to farm animals, animal fertilizer use, consumption of nonbottled water. Statistically significant estimates are italicized.

‡At least 10 ducks were kept by 11 cases and 10 controls (MVRR *3.9*, 1.4-11).

§No subjects reported using human waste as fertilizer.

‖Cattle or water buffalo (15 cases, 24 controls; 1 case and 1 control did not report exposure to farm animals), chickens (5, 11); ducks (4, 3); pigs (3, 2).

Table 7. Sources of drinking water among 257 cases of aplastic anemia and 1087 controls according to region; phase 2 data only

Source	Cases		Controls		Relatie risk estimate	
	No.	%	No.	%	Crude	Multivariate* (95% CI)
Bangkok; 77 cases, 317 controls						
Bottled/distilled water only	25	32	102	32	1.0†	1.0†
Other sources§	52	68	215	68	1.0	1.0 (0.6-1.8)
Well water	2	3	1	0.3	—	—
Tap water	10	13	55	17	0.7	0.8 (0.3-1.7)
Rain water	3	4	24	8	0.5	0.5 (0.1-1.9)
Boiled water	28	36	82	26	1.4	1.6 (0.8-3.2)
Other	5	6	13	4	1.6	1.7 (0.5-5.2)
Khonkaen; 180 cases, 770 controls						
Bottled/distilled water only	9	5	115	15		1.0†
Other sources‡	171	95	655	85	3.3	*2.8* (1.3-5.9)
Well water	18	10	42	5	5.5	*3.5* (1.4-9.2)
Nonartesian water only	13	7	26	3	6.4	*3.7* (1.3-11)
Tap water	8	4	25	3	4.1	*3.8* (1.2-12)
Rain water	141	78	563	73	3.2	*2.6* (1.2-5.6)
Boiled water	15	8	50	6	3.8	*2.9* (1.1-7.7)
Other	2	1	16	2	—	—

— indicates not calculated.

*The following factors were included in the models: Bangkok: age, sex, year of interview (continuous term), consumption of nonbottled water; Khonkaen: age, sex, residential location, year of interview (continuous term), pesticide use, exposure to ducks, animal fertilizer use, consumption of nonbottled water. Statistically significant estimates are italicized.

†Reference category.

‡Categories not mutually exclusive.

formal epidemiologic studies have been undertaken only recently. The IAAAS established a widely accepted annual incidence of 2 per million for Europe and Israel[26]; similar figures were obtained elsewhere in Europe.[35-37] In the first phase of the present study, based on similar methodology to the IAAAS, we determined a stable rate of 3.9 per million for the Bangkok metropolitan area and in Khonkaen, 5 per million.[27] Other Asian series have produced a range of 5 to 7 per million.[38] Marked variations in the frequency of the disease, sometimes even within the same country or region, are suggestive of environmental factors influencing the occurrence of AA.

The salient findings in this study were associations of AA with a number of known or strongly suspected risk factors, and associations with some environmental factors not previously linked to the disease. Relative risk estimates ranged from 2.0 to 7.4. Previously reported factors included benzene and other solvents, pesticides, and certain specific drugs, including sulfonamides, mebendazole, and thiazides. For chloramphenicol, the data were sparse, and the point estimate was modestly elevated but not statistically significant. Factors that had not been reported previously included exposure to ducks and geese, the use of animal fertilizers among farmers, and nonmedical use of needles. We also observed a marked increased risk associated with use of nonbottled water in the Khonkaen region. Finally, there was a strikingly infrequent occurrence of posthepatitis AA.

In contrast to our previous report from phase 1 of the study,[29] low income was no longer associated with AA. Inadequate control for confounding could have explained the relationship observed earlier; alternatively, low income may have initially reflected causal exposures, which changed over time. The latter possibility is plausible because there was considerable economic development in Thailand during the study period.

The positive association with benzene was anticipated, although few cases related a history of exposure. Marrow failure has been detected readily among Italian shoe workers in the 1950s[39] and Chinese workers in a variety of industries in the 1960s.[40,41] While industrial use of benzene has long been linked to bone marrow failure, the historical nature of the record and the recognition of other hematologic sequelae of chronic exposure has cast doubts on the accuracy of the early descriptions.[42] Mild blood count abnormalities occur with benzene exposure[43] and may have been incorrectly equated with AA in some surveys.[44-46] While several decades ago benzene exposure appeared to account for a large proportion of AA causation in certain regions,[47,48] it does not appear as a major risk factor in more recent population surveys or in clinic series. In the IAAAS, only about 5% of cases reported benzene exposure and another 3% petrochemical exposure, and benzene therefore was only a borderline risk factor.[26] Chemical exposure was a risk factor in the French epidemiologic report.[49] A recently published analysis of Chinese workers has suggested that even low levels of benzene can induce hematotoxicity.[50]

We did not observe a convincing association between AA and exposure to specific solvents other than benzene, despite a questionnaire designed to elicit such details. However, the risk estimate was significantly elevated for overall exposure to solvents other than benzene, glues, and fuels, mostly to unspecified thinners. Turpentine was the chemical most frequently mentioned, but any possible association was confined to fewer than 4 days of cumulative exposure. We consider it improbable that a true causal association would not also be present for more substantial exposure. Despite early case reports implicating a variety of chemicals in the causation of AA, the limited numbers of population-based studies have not confirmed the clinical literature for such diverse agents as hair dyes,[51] glycol ethers,[52] or Stoddard's solvent.[53] In a recent study of environmental factors performed in the United Kingdom, exposure to solvents and degreasing agents was common among both cases and controls, but showed only a borderline association with AA.[54]

In the Khonkaen region, we observed significant associations with several pesticides, including organophosphates, DDT, and carbamates, and a borderline association with paraquat. In the IAAAS, occupational insecticide use also was a risk factor for AA (overall relative risk, 3.7), although relatively few patients had been exposed (5% of cases compared to 2% of controls).[26] Lack of

evidence of an association with household pesticide exposure in the present study may indicate a dose relationship, but different chemical formulations often are employed for home compared to agricultural use. Other epidemiologic data concerning pesticide exposure and AA are weak. There are large numbers of patient histories anecdotally relating AA to pesticides.[55] The British case-control study identified an overall 2.5-fold increase in risk with occupational exposure, but specific pesticides were not evaluated. There also was a 5-fold increase in risk among adults whose homes were treated for woodworm.[54] Individual pesticides have been implicated in disease causation, including, particularly, the chlorinated hydrocarbons, organophosphates, chlorophenols, and pyrethins.[56-59] Agricultural carbamates have not been associated previously with AA. We reported a possible association with household insecticides in this class from phase 1 of the present study[31] that was not observed in the phase 2 data. Dose-related toxicity has not been supported by surveys of individuals most likely to be heavily exposed, including manufacturers,[60-63] applicators,[64-67] or farm workers,[68,69] with only rare exceptions.[70,71]

Of all drugs, chloramphenicol has been the agent most prominently associated with AA.[2,72,73] In the 1950s and following decades, the drug was considered to be the most common cause of the disease.[74,75] In the current study, chloramphenicol was infrequently used and there was no significant association; however, the numbers were insufficient to exclude an increased risk. Earlier studies suggesting that chloramphenicol increases the risk of AA have been criticized. Almost certainly, the evidence from adverse reaction report registries was biased by a selective tendency to report exposed cases, and the earlier epidemiologic studies were methodologically unsatisfactory. Chloramphenicol is inexpensive and effective and continues to be a popular drug in certain parts of the world. Based on the present findings, we concur with the view that the risk of AA in chloramphenicol users was probably overstated in the past.

For other drugs, the present findings resemble those described in phase 1,[32] but for sulfonamides, mebendazole, and thiazides, the relative risk point estimates based on the full data, while significantly elevated, were all lower. For NSAIDs, the relative risk estimate of 1.6 was compatible with some very modest increase in risk but nonsignificant. In the IAAAS,[26] sulfonamide use was associated with AA, and the use of thiazide diuretics was not, and there was no mebendazole use; several NSAIDs were significantly associated with AA. The presently identified associations with sulfonamides, thiazide diuretics, and mebendazole can, at most, account only for a small proportion of the occurrence.

Several of the novel risk factors identified in the current study of AA, especially the farm exposures to ducks and geese, animals that can serve as zoonotic reservoirs for viruses, and the consumption in Khonkaen of water from nonbottled sources, which could account for most cases there, are suggestive of exposure to an infectious agent. Alternative explanations for the association with nonbottled water also should be noted, including chemical contamination of water supplies and unidentified lifestyle factors that could not be allowed for in the analysis. The potential relationships with the use of animal fertilizers and nonmedical needle exposures provide further evidence for an infectious etiology, which has been suspected for AA on several grounds. Clinically, marrow failure can represent a rare but serious sequela of certain specific infections, especially following Epstein-Barr virus infection and infectious mononucleosis[76] and after seronegative hepatitis.[77] Postviral AA is responsive to immunosuppressive drugs, consistent with an immune mechanism of marrow cell destruction[78]; indeed, the involvement of activated cytotoxic lymphocytes and cytokines is the normal pattern of the immune response to a large variety of viral agents. Many other autoimmune diseases have postulated but unknown infectious triggers. Some of the chemicals and drugs historically associated with AA on the assumption of direct toxicity for hematopoietic cells might be surrogates for infectious exposure: pesticides for an insect vector and chloramphenicol or NSAIDs for a preceding febrile illness are examples. In the first epidemiologic study of AA, an American medical officer at the end of World War II noted the surprisingly large number of cases of AA among soldiers serving in the Pacific (6.6-28.4/million) compared to numbers reported for those elsewhere (0.4 to 1.8/million).[79] While Custer blamed this enormous difference on atabrine malaria prophylaxis, this agent has been linked to only a handful of cases of AA; equally plausible is the possibility of exposure of a naive group to an endemic, geographically limited agent.

Posthepatitis AA syndrome accounts for about 10% of marrow failure in Western case series.[77,80] Strikingly, in the current study, hepatitis was virtually absent in the medical history of cases in Thailand. This observation is particularly puzzling, as acute seronegative hepatitis (non-A, non-B, non-C, non-E) is far more frequent in Asian hepatology clinics, where it may represent approximately 20% of cases,[81] than in the West, where the frequency is only a few percentage points.[82] Differences in host response may be linked to the immune system, as HLA B8, strongly associated with posthepatitis AA among American patients,[83] is a rare histocompatability antigen in Asian populations.

The overall validity of the present findings must be interpreted in the light of the following considerations: first, some identified associations are based on small numbers, and statistical significance notwithstanding, may be fragile and susceptible to error due to misclassification. The identification of organic solvents, a large proportion of which could not be specified by the subjects, or individual pesticides, for example, sometimes could be mistaken. When numbers were large, random misclassification or underreporting would generally result in attenuation of the magnitude of the observed associations, but when the numbers were small, that assumption may not hold even for relatively large relative risk point estimates, and they must be interpreted cautiously. The possibility that misclassification or under-reporting, particularly for occupational exposures that might not be recognized by subjects, could have resulted in failure to identify some associations also must be considered. For solvent and pesticide exposures, in general, risk estimates for higher cumulative exposure were similar to the overall risk estimates; while possibly indicating misreporting of the amounts of exposure, a dose-response might not be evident due to the small numbers of exposed subjects or to the presence of a (low) threshold effect.

Second, some apparent associations could have been due to bias or confounding. Information bias could have occurred if the interviewers or the subjects, especially the cases, were aware that substances such as benzene or other chemicals may cause AA. All subjects were interviewed shortly after hospital admission (the median interval was 3 days for cases and 2 days for controls), and the interviews and questionnaires were highly structured, rendering information bias less likely but impossible to exclude completely.

Selection bias was generally unlikely. Bias due to refusal to participate was not present: there were no refusals. With regard to the identification of the cases, the definition of AA was standardized and rigorous: virtually all cases were prospectively identified, and the study was population based except in Bangkok, phase 2, where selection bias could have occurred if cases admitted to

Table 8. Etiologic fractions for various factors associated with aplastic anemia in Thailand

Factor	Relative risk estimate	Proportion of cases exposed, %	Etiologic fraction, %
Benzene	3.5	1	1
Other organic solvents*	2.0	11	5
Associated drugs†	3.9	4	3
Agricultural pesticides (Khonkaen)‡	3.5	22	15
Exposure to ducks (Khonkaen)§	3.7	26	19
Use of animal fertilizers (Khonkaen)§	2.1	27	14
Use of nonbottled water (Khonkaen)	2.8	95	61
Nonmedical needle exposures	3.8	3	2

Based on all factors with elevated relative risk estimates and lower confidence limits of 1.0 or greater that represent direct exposures (Results; Tables 3-7). The factors are not mutually exclusive, and therefore the individual etiologic fractions cannot be summed to determine the total proportion of aplastic anemia that can be explained.

*Not including fuels or glues.

†Sulfonamides, mebendazole, and thiazide diuretics.

‡Organophosphates, DDT, carbamates, paraquat.

§Among farmers, farm workers, or those who live on farms.

Siriraj Hospital differed in their exposure status from cases admitted to other hospitals. Bias in the selection of controls was improbable because subjects were eligible for inclusion only if they were admitted for conditions unlikely to be related to putatively causal agents.

Allowance was made for potential confounding by several factors, including age, sex, residence, year of interview, and exposures associated in this study with AA (such as various pesticides) or identified as possible causes in the literature (such as benzene). Nevertheless, since it is possible that many of the environmental causes of AA remain unknown, residual confounding by unidentified factors cannot be ruled out. In addition, when numbers of exposed subjects were small, the multivariate models used in the analysis may have been unstable, and adjustment for confounding may have been inadequate.

Etiologic fractions are shown in Table 8 for all factors that were significantly associated, based on relative risk estimates reported in "Results." Previously suspected risk factors accounted for only a small proportion of the occurrence of AA in Thailand, especially in comparison to Western series. None of the agents implicated historically—benzene, chloramphenicol, and other drugs—could explain the higher rate of marrow failure that we observed. Novel factors—water source, animal exposure, use of animal fertilizers, and nonmedical needle exposures—could account for a large proportion of cases in Khonkaen, and point to an infectious etiology. Pesticides, which may themselves be toxic to marrow, might also represent surrogates for an infectious exposure, as through an insect vector. In addition, these factors may partly explain the higher incidence of AA in rural Khonkaen compared to Bangkok, and possibly also the high incidence in Asia compared to the West. The findings also suggest future research to identify a putative infectious agent as well as genetic risk factors for disease and the use of molecular laboratory assays in the context of population-based studies.

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Appendix

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